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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,693	BERLIN ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6 and 8-16* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/03/2008 has been entered.

2. Currently Claims 1-4, 6, 8-16 are pending. Claims 5 and 7 have been cancelled. Claim 15 has been withdrawn.

3. The following is a nonfinal action rejection of claims 1-4, 6, 8-14, and 16. Response to arguments follows the rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-4, 6, 8-9, 14, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-4, 6, 8-9, 14, and 16 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the process steps of the claims. The preamble states a method of detecting the presence of a disease characterized by an increased amount of organ-specific free floating DNA, whereas the last step is

detecting the amount of presence of free floating DNA. Therefore there is no required step of measuring an increased amount of organ specific free floating DNA, but rather just the determination of the presence of such DNA. Therefore it is not clear if the claims mean detecting the amount of a disease characterized by an increased amount of organ specific free floating DNA or determining the presence of such DNA.

Claim Rejections - 35 USC § 112/Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6, 8-11, 13-14, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the art does enable one of skill in the art to analyze cytosine methylation in free floating DNA neither the art nor the specification enables one of skill in the art to determine the presence or absence of ANY cellular proliferative disease in a tissue, cell type or organ.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have

been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

The claims are drawn to a method of determining the fraction of total free floating DNA in a bodily fluid that originates from a specific organ comprising obtaining a bodily fluid, subjecting the free floating DNA to methylation and determining the amount or presence of free floating DNA that originates from a particular organ with that of a normal control value and detecting an disease characterized by an increased amount of organ specific free floating DNA. The claims are further drawn to comparing the total amount of free floating DNA and the fraction of free floating DNA that originates form the organ and detecting an disease characterized by an increased amount of organ specific free floating DNA. The claims are further drawn to determination of an increased amount of free floating DNA that originates from an organ and detecting an disease characterized by an increased amount of organ specific free floating DNA.

Therefore the claims are drawn to diction of the presence or an increase amount of free floating DNA originating from a particular organ and correlating the detection with the presence of any disease characterized by an increased amount of organ-specific free floating DNA.

Nature of the Invention

The claims are broadly drawn to a method of determining any DNA methylation pattern for any organ and detection of the presence of any disease. The claims broadly encompass determining the presence of ANY diseased condition that originates from ANY organ by detection of the presence of any type of methylation pattern. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification asserts a means to predict which organ has developed a medical condition, by employing means of distinguishing between DNA originating from different healthy or different organs of the human body (p. 19 last paragraph). The specification asserts characteristic methylation patterns of certain genes can be positively correlated with specific organs (p. 19 last paragraph).

The specification does not provide a predicative association of the detection of any disease by the detection methylation patterns. The claims encompass the phrase "a disease characterized by an increased amount of organ-specific free floating DNA". This phrase would encompass the specific detection of a specified disease associated with an increased amount of organ-specific free floating DNA. For example it would

encompass the detection of any type of cancer, any hypertensive disease, any cirrhosis-based disease, any neurological disorder associated to the organ, to name a few. It is noted that Claim 16 limits "a disease characterized by an increased amount of organ-specific free floating DNA" to cancer types. Therefore it is clear that the claims can be broadly interpreted to determination of specific types of disease. As discussed below, the instant specification has not provided any specific correlation to a methylation status of an organ and a specific disease. As shown by the art provided below associations of methylation status and disease is unpredictable.

The specification asserts the knowledge achieved allows predicting if the individual carries a medical condition, such as a cell proliferative disease in said organ (p. 22 5th paragraph). The specification asserts a patient with a substantial amount of free floating DNA originating from liver, might have developed a liver tumor (p. 22 5th paragraph). The specification asserts that to validate this, the next step could be to employ, for example, a tailored test assay for disease indicating marker gene expression, specific for said organ or tissue (p. 22 5th paragraph). Therefore the specification asserts that validation studies are sometimes needed to clearly associate detection of free floating DNA with detection disease.

The specification asserts that methylation patterns found in the tested sample will be identified as belonging to a certain organ (p. 34 5th paragraph). The specification asserts that methylation patterns can be associated either by comparing the individual data set resulting from said analysis to data received in previous studies or to a dataset obtained in a parallel experiment on one or preferably more control fluids (p. 34 last

paragraph). The specification indicates that to determine if methylation patterns are associated with disease a comparison study must be done, however, the claims as broadly written, merely comprise the detection of methylation patterns.

The claims are drawn broadly to the determination of any methylation status of the organ, which would include detection of the presence of methylation, decreased methylation, and increased methylation. However, the instant specification has not provided a predictable determination of detecting the presence of a disease characterized by an increased amount of organ specific free floating DNA and the detection step of detecting any type of methylation status. Therefore it would be unpredictable to correlate disease characterization based upon any methylation status of an organ.

Post filing art, Cottrell (clinical Biochemistry 2004 Vol. 37 p. 595) teaches that because methylation-based markers are not routinely used in clinical labs, the methodology has not been fully optimized, validated, and standardized. Cottrell et al. teaches that most of the methylation methods rely on bisulfite treatment protocol which must meet strict requirements for consistency and performance (p. 601 1st column 2nd full paragraph). Cottrell et al. teaches that in order to discover optimal markers and create successful assays, there will need to be clearly defined clinical questions, sample sets, and methodologies coupled with the current methylation technologies (p. 601 1st column last paragraph). Based on the data presented in the specification and the teachings in the art, it is unpredictable to correlate the methylation pattern of any free floating DNA to ANY disease condition by detecting methylation patterns. The art

teaches the lack of predictability with regard to methylation pattern studies and correlation to any disease condition.

Figure 7 is disclosed in the specification as the result of the study wherein DNA methylation pattern of specific CpGs in DNA from four different tissues has been analyzed (p. 42). The specification discloses that methylation analysis from CpG positions correlate to the specific tissue types (p. 43). However, the art as exemplified by Cottrell et al. teaches that using circulating DNA as a diagnostic tool is unpredictable and that methylation patterns are not reproducible. Therefore the specification, even though it shows that one can detect methylation positions, does not provide guidance as how to use such methodology to detect the presence of a disease derived from the organ.

In summary, the claims encompass the detection of any disease using samples from by the detection of free floating DNA or the detection of methylation patterns of free floating DNA, however, the specification does not provide guidance as to how to make associations between any disease in an individual by the detection of free floating DNA. Moreover, the specification indicates that the correlation of disease and free floating DNA must have an association step to compare to a validation study. The associations are unpredictable, because the specification provides no statistically significant association between any disease and detection of free floating DNA, further the art teaches that theses associations are unpredictable.

Working Examples

The specification provides no examples to correlate detection of a specific

disease by detection of free floating DNA in any individual. Example 1 describes determining plasma blood from one patient to detect neoplastic disease (p. 43). The specification asserts that it was concluded a significant portion of the DNA in the patient's blood derived from his lung, the physician now referred the patient to a hospital that is specialized on inflammatory or cell proliferative diseases of the lung. However, the specification does not provide any pvalue, therefore, it is unclear how to extrapolate the example of one specific patient to the detection of a large portion of DNA derived from lung to the detection of any disease by detection of free floating DNA.

The specification asserts three more patient samples with detection of serum DNA levels (p 43-44), however there are no working examples showing a statistically significant association of any disease. The first three experiments only had an association of a specific patient and a specific disease, whereas it is unclear the number of patients in the 4th experiment.

Furthermore, the specification provides no indication as to whether the detection of a methylation pattern is significant such that the skilled artisan would be able to predictably correlate the results which any disease condition. The specification does not have an example of determining in any sample a correlation of methylation pattern with detection or ANY diseased condition.

Therefore, though the specification provides a few studies of the correlation of one patient and the detection of one tissue type and as presented in figure 7 the correlation of specific CpG island methylation patterns and organ type, the art as discussed above teach that these associations are unpredictable. Further, the guidance in the specification only indicates that an increased level of organ specific free floating DNA is indicative of an organ based disease, but not a specific disease. Further, it is well known that some disease have effects on multiple organs. For example, Paredes-

Zaglul et al. (Clinical Cancer Research Vol. 4 April 1998 p. 879) teaches that colon cancer spreads to the liver (p. 879 2nd column 1st paragraph). Therefore it would be unclear if an elevated free floating DNA amount in the liver would be indicative of a liver based disease or rather a colon based disease. The art teaches that the correlation of methylation patterns to any disease in any given population is not reproducible. The skilled artisan, therefore, would have to perform undue experimentation in order to determine if methylation patterns in circulating DNA is correlative to any disease.

The predictability or unpredictability of the art and degree of experimentation

The art teaches that there is unpredictability in associating circulating DNA (free floating) with disease. The post-filing art, Bremnes et al. (Lung Cancer 2005 Vol 49 p. 1) teaches a review of circulating DNA in lung cancer by evaluating the role of circulating DNA in 22 studies (abstract). Bremnes et al. teaches the analysis of circulating DNA in plasma might lead to increasing clinical impact, however, large perspective clinical studies are needed to validate and standardize any test for DNA alteration in plasma or serum of high risk individuals or patients with established lung cancer (Abstract). Therefore there is still unpredictability with correlating circulating DNA in plasma and serum with disease condition. The combined data from those studies indicated that circulating DNA levels were increased in about 61% of the cancer cases. Similarly, the methylation levels of different genes varied from 5 to 73%, depending on the gene (Table 4; page 8, third paragraph). In conclusion, the authors state (Abstract):

"The analysis of circulating DNA or RNA in plasma is a promising non-invasive diagnostic tool, requiring only a limited blood sample. Its wide applicability and potential importance will possibly lead to increasing clinical impact in the near future. However, large prospective clinical studies are needed to validate and standardize any tests for DNA or RNA alteration in plasma or serum of high risk individuals or patients with established lung cancer."

Therefore, circulating DNA and its relationship to cancer diagnosis remains an interesting clinical research topic, but not a diagnostic tool.

Jung et al. (Cancer Letters 2004 Vol 205 p. 173) teaches the presence of circulating DNA (free floating) in patients with prostate cancer and benign prostate hyperplasia (BPH) (abstract, page 174-175 1st two paragraphs). Juang et al. teaches that patients with metastases had higher levels of circulating DNA, the DNA levels in cancer patients without metastases were not significantly different from the normal controls, whereas some of the BPH patients had circulating DNA levels higher than normal (p. 175-176 and Figure 2). Therefore Jung et al. indicates that that circulating DNA levels vary according to the disease, whereas cancer patients had different levels of circulating DNA compared to patients with metastases. Therefore it is unpredictable that comparison of circulating DNA to a control would indicate a particular disease.

As evidenced by current literature, circulating DNA is not always correlated with the presence of cancer in a subject. Sidransky et al. (Ann. NY Acad. Sci.,2000 vol. 906, pp. 1), the origin of circulating DNA in the blood is uncertain (page 3, second paragraph), and "these studies raise significant issues about the biology and physiology

of how the DNA is released and maintained in the circulation and ultimately on its clinical value" (page 3, third paragraph). Sindransky states further "However, it is abundantly clear that large prospective studies with longitudinal follow up are essential if we are to carefully evaluate these circulating DNA markers and eventually integrate them into the clinical setting." Therefore elevated DNA levels are not indicative that the patient has any particular organ based cancer, but rather an indication that other validation studies must be performed.

The current art teaches that methylation is not only caused by neoplasms, but that methylation can be detected in normal tissue. This indicates that detection of methylation does not indicate neoplasic tissue. The current art teaches detection of methylation is indicative of not only neoplasm but also aging of normal cells. Yates et al. (Oncogene 2006 Vol 25 p. 1984) teaches that methylation increases with age and malignancy (abstract). Yates et al. teaches that methylation was detected in urine DNA from patients with and without bladder cancer (Abstract). Yates et al. teaches aberrant methylation is not cancer specific and can be found in a normal ageing cell population (p. 1985 1st column 1st paragraph). Yates et al. teaches the overall knowledge of the molecular mechanisms of DNA methylation in health and cancer remains poor and one uncertainty is the extent of aberrant DNA methylation in nonmalignant tissue and the association between ageing and aberrant DNA methylation (p. 1985 last paragraph). Therefore in a given patient elevated free floating DNA from a particular organ compared to a normal control might be indicative of the aging of the patient rather than a particular disease.

Lui et al. (Clin Chem Lab Med 2002 Vol. 40 p. 962-968) teaches that circulating DNA is present in increased amounts in transplant patients (p. 963 last two paragraph and p. 964 1st paragraph) and in trauma patients (p. 964 2nd paragraph). Therefore the presence of cancer is not the only source of circulating DNA in the body. Further, medical transplantation and physical trauma can effect an individual's free floating DNA level, therefore it is unclear if an elevation compared to a normal control is indicative of a particular disease, or rather a physical trauma which has occurred on the patient's body.

The art presented shows the unpredictability of determining the methylation profiles of organs and tissues for comparison to detect cellular proliferation. Eckhardt et al. (Nature Genetics 2006 Vol. 38 p. 1378) teaches methylation patterns for three human chromosomes from a representative number of healthy human tissues and primary cells (p. 1378 2nd column 1st paragraph). Eckhardt et al. teaches methylation patterns are influenced by a number of endogenous and exogenous parameters (p. 1381 1st column last paragraph). Eckhardt et al. teaches that tissue (e.g. organ) samples may be inherently more heterogeneous than primary cells because of the different cell types constituting a given tissue (p. 1382 1st column 2nd paragraph). Eckhardt et al. teaches that some tissue such as lung and colon will show a stronger correlation between age and methylation (p. 1382 1st column 2nd paragraph). Therefore the postfiling art teaches determining a methylation pattern that is characteristic for a particular tissue, cell type or organ to detect the presence of a cellular proliferative disease is unpredictable. Eckhardt et al. teaches that different

profiles can be obtained depending on the age. Eckhardt et al. teaches that the profile of some tissues contains heterogeneousity because of the varying cell types in the tissue. Eckhardt et al. teaches that tissue samples may be inherently more heterogeneous than primary cells because of the different cell types constituting a given tissue (p. 1382 1st column 2nd paragraph). Eckhardt et al. teaches that some tissue such as lung and colon will show a stronger correlation between age and methylation (p. 1382 1st column 2nd paragraph).

Raykan et al. et al. (PLOS Biology December 2004 Vol. 2 p. e405) teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (e.g. organs) (p. 2171 2nd column last paragraph). Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and disease state (p. 2176 last paragraph). Therefore Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a particular tissue, cell type, or organ without determining the differences in the methylation patterns between individuals. In other words, it would be unpredictable that the level of free floating DNA detected was from a particular tissue type or from differences between individuals.

Therefore the comparison of a sample in one patient to a profile might indicate that there is a high level of certain methylation sites, however, this methylation pattern could be due to developmental stage, age, and disease state of the patient.

Dennis et al. (US Patent Application Publication 2003/0044388 March 6, 2003 filed August 31, 2001). Dennis et al. teaches obtaining a bodily fluid from a human sample (e.g. plasma or serum) (p. 2 paragraph 9). Dennis et al. teaches detecting the amount of DNA (e.g. in plasma and therefore free floating) that originates from a particular organ comprising analyzing a DNA methylation pattern p. 2 paragraph 9). Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the disease is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches comparisons of the methylation status with control subjects (paragraph 43 p. 5). It appears that the teachings in Dennis et al. and the instant specification are commensurate, however, the specification does not appear to add anything further to the teachings of the prior art. Based upon the evidence presented in the instant specification it is not clear that the instant specification provides enabling support, however, if the specification is found to be enabling, in order to have compact prosecution an 35 USC 102 rejection has been made over Dennis et al. and is presented below.

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate detection of any disease by the detection of free floating DNA. The specification discloses that a correlation to disease must include an association step to compare methylation patterns to individuals and a validation study to confirm detection of

disease.

The art teaches detection of disease with methylation patterns in free floating DNA is unpredictable and that these associations need to be confirmed by multiple large sampling sizes to determine a clear association. The skilled artisan, therefore, would have to perform undue experimentation to determine the correlation of disease detection to detection of free floating DNA as it is broadly written in the claims.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written. The skilled artisan would have to determine the association of any detection of disease with measurement of free floating DNA. The skilled artisan would then have to determine if this association was species base. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he

scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide any predictable association of detection of free floating DNA and any disease. Further the art teaches that the measurement of free floating DNA and associations made are unpredictable. In view of this unpredictability, the specification has not established that the presently claimed method can be used to determine the detection of any disease by the detection of free floating DNA or methylation patterns of free floating DNA.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Arguments

The reply traverses the rejection. A summary of the reply is presented below with response to arguments following. The reply summarizes the 35 USC 112 rejection presented in the final rejection (1/03/2008) (p 7-10). The reply provides relevant law (p. 10 last paragraph- 11). The reply summarizes the amendments made to the claims and

point to the disclosure for support (p. 11 last paragraph -p. 13).

(A)The reply asserts that there has not been a prima facie case of lack of enablement because the degree of experimentation is not undue experimentation but rather routine experimentation (p. 11 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Though the skilled artisan would be able to perform a method of determining the amount of free floating organ DNA in a sample, it would be unpredictable to use such a method to predict a disease as exemplified by the claims. As shown above, the specification does not provide a specific example of detection of any specific disease, whereas the art teaches that such correlations are unpredictable. For example, as discussed above Raykan et al. et al. (PLOS Biology December 2004 Vol. 2 p. e405) teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (e.g. organs) (p. 2171 2nd column last paragraph). Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and disease state (p. 2176 last paragraph). Therefore Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a particular tissue, cell type, or organ without determining the differences in the methylation patterns between individuals. Such experimentation is not routine, but rather, requires the skilled artisan to perform many experiments on different samples with many intervening steps without a guarantee of success. Therefore as discussed

above, the experimentation required would be considered unpredictable based upon the lack of guidance in the specification and the unpredictable with such associations as exemplified by the cited art.

(B) The reply asserts that the claims are drawn to the characterization of any disease of an organ by the detection of a disease characterized by an increased amount of organ specific free floating DNA and therefore the method does not require further methods to detect specific disease of the organ (p. 14 1st paragraph). The reply asserts that the correlation is the amount of free floating DNA originating from an organ is associated with a diseased organ without correlation of the characterization of the disease (p. 14 1st paragraph).

The reply asserts that a comparison to a normal control is not required for the claimed method but has been amended into the claims (p. 14 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be asserting that the claims are drawn to a general determination that there is disease present in an organ and a specific disease is not required to be detected. However, the claims are not limited to a general determination that a disease is present in an organ, but rather the claims specifically set forth detecting a disease and this encompass the embodiment of detection of a specific disease derived from an organ. This is further evidenced by Claim 16 which specifically limits the disease to cancer. Therefore it seems clear that detecting the presence of a

disease characterized by an increased amount of organ-specific free floating DNA would encompass the detection and determination of a specific disease. As shown above the specification clearly indicates that such determinations require further validation studies (p. 22 5th paragraph).

Though the limiting step of comparison to a normal control value has been added to the claim limitations, this limitation is not sufficient to overcome the unpredictability in the art. As shown in Lui et al. (circulating DNA is present in increased amounts in transplant patients (p. 963 last two paragraph and p. 964 1st paragraph) and in trauma patients (p. 964 2nd paragraph). Medical transplantation and physical trauma can effect an individual's free floating DNA level, therefore it is unclear if an elevation compared to a normal control is indicative of a particular disease, or rather a physical trauma which has occurred on the patient's body. Further as shown in Raykan et al. DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and disease state (p. 2176 last paragraph). Therefore the art is clear that individual methylation levels vary based not only on disease state but on trauma of the body, developmental stage, and organ type. Therefore a comparison to a normal individual will show elevated free floating DNA that is not correlative to a disease, but rather a physical attribute of the patient.

(C) The reply asserts that though the applicant agrees with Cottrell et al. assertions, the teachings in the instant specification in combination with the skill in the

art provide support to detect diseases of particular organs that are accompanied by an increased level of a particular organ specific DNA in the blood of body fluid (p. 15 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Based on the data presented in the specification and the teachings in the art, it is unpredictable to correlate the methylation pattern of any free floating DNA to ANY disease condition by detecting methylation patterns. The art teaches the lack of predictability with regard to methylation pattern studies and correlation to any disease condition in general. Therefore the art does not provide guidance to particular detection of disease with methylation patterns, further the specification does not provide guidance to overcome the unpredictability found in the art because the specification does not provide guidance to specifically detect any disease characterized by an increased amount of organ specific free floating DNA that originates from an organ. Though Cottrell et al. does not teach the unpredictability of methylation detection in particular organs, it does teach in general methylation is unpredictable. Further, Raykan et al. et al. (PLOS Biology December 2004 Vol. 2 p. e405) teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (e.g. organs) (p. 2171 2nd column last paragraph). Therefore the art teaches that even in the specific embodiment of organ specific methylation status, there is unpredictability.

(D) The reply asserts that the teachings of Ziegler et al. are irrelevant (p. 15 2nd

paragraph). The reply asserts that it does not matter that the amount of tumor DNA circulating in the plasma is highly variable because this is not the fraction of DNA that is contributed by the affected organ which is what the claim is now drawn to (p. 15 3rd paragraph-p. 16 1st paragraph). The reply asserts that though Ziegler et al. teaches that methylation studies are not always reproducible, there are many art recognized examples demonstrating the reliability of detecting methylation patterns using suitable markers to show predictable support (p.16 2nd paragraph).

It is noted that based upon the amendments to the claims the reference of Ziegler et al. has been removed from the above 35 USC 112/Enablement rejection and therefore the arguments presented are moot.

(E) The reply asserts that the art which shows the unpredictability and degree of experimentation as presented in the final rejection might show the unpredictable variation in the total amounts of free floating DNA but it is irrelevant because the claimed method comprising a correlation between organ specific circulating DNA and disease of said organ (p. 17 1st paragraph). The reply asserts that the clinical value of the total amount of circulating DNA may be questionable or unpredictable the analysis of organ specific fractions therein is highly informative (p. 17 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive. In general, methylation in free floating DNA is unpredictable. Further, the art provides guidance that organ specific free floating DNA methylation status is unpredictable for disease determination. Raykan et al. et al. (PLOS Biology December

2004 Vol. 2 p. e405) teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (e.g. organs) (p. 2171 2nd column last paragraph). Therefore the art teaches that even in the specific embodiment of organ specific methylation status, there is unpredictability. Therefore the art of record, clearly shows relevant unpredictability for the claimed method. Though organ specific fractions might be informative, there is unpredictability as to what information can be ascertained by the detection. The claims encompass the method of detecting a specific disease, whereas the instant specification clearly shows that such a determination requires further validation studies. As to the general embodiment of any disease characterized by increase amount of organ specific free floating DNA, Raykan et al. teaches that such determination is unpredictable based upon the differences observed in methylation status between not only organs but individuals. Further, Paredes-Zaglul et al. teaches that colon cancer spreads to the liver (p. 879 2nd column 1st paragraph). Therefore it would be unclear if an elevated free floating DNA amount in the liver would be indicative of a liver based disease or rather a colon based disease.

(F) The reply asserts that that though it is know through the teaching of Yates that methylation patterns may not only be indictable of cancer but of other informative information, the claims are drawn to the determination of a particular pattern of an organ status regardless of the age status (p. 17 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Age status, however, would affect the amount of circulating DNA and therefore would be an unpredictable factor in the comparison of a sample with a normal control. It would be unpredictable that the differences between the two were based upon an organ specific disease, or rather based upon age differences between the sample and the normal control. Therefore patterns of organ status would be affected by the age of the sample and therefore the skilled artisan would have to determine if difference are based upon a disease of the organ or based upon a physical characteristic of the patient.

(G) The reply asserts that statements about the amount of direction or guidance provided by the specification are misleading because the specification teaches that an increased level of organ-specific circulating DNA is indicative of diseased organ (p. 18 1st paragraph).

The reply assert that such correlations do not have to include an active association step to compare methylation patterns to individuals but simply to compare methylation patterns or methylation analysis results with appropriate samples (p. 18 2nd paragraph) such that the amendments of comparison of a normal control value removes said unpredictability (p. 18 4th paragraph).

The reply asserts the specification does not indicate that a correlation must include a validation study to confirm detection of disease, but rather it is an option to further analyze the organ once it is identified (p. 18 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The specification asserts that an increased level of organ specific circulating

DNA is indicative of a diseased organ, however, the art clearly teaches that increased levels of organ specific circulating DNA can be indication of other physical characteristics of the sample (see the teachings of Raykan et al. and Lui et al.). Therefore an increased level of circulating DNA is not always directly correlative to a diseases organ.

The reply indicates that no active association step is required but simple a comparison of a normal control value to the methylation status of organ specific DNA. The claim language states that determining happens "based on" comparing. However, as discussed above, other physical attributes of a sample affect methylation status such that increased methylation status is not always indicative of only diseased organs but also of differences in age and physical trauma.

The reply asserts that a validation study is only an option to further analyze the organ once it is identified, however, the claims include the embodiment of specifically detecting a disease associated with the organ. As such the skilled artisan would have to further perform validation studies, as disclosed in the specification, to specifically detect a particular disease as the art shows that such correlations are unpredictable based solely on methylation status.

(H) The reply asserts that all the Wands factors have not been considered because the experimentation needed to perform the claimed method is merely routine experimentation and not unpredictable (p. 19 1st full paragraph-last paragraph). The reply asserts that there is insufficient evidence that the required experimentation is

anything other than routine (p. 19 last paragraph).

The reply asserts that the skill in the art at the time of filing was high and therefore determination of methylation state of one or more CpG residues relative to a control could be performed by one of skill in the art (p. 20 1st paragraph).

The reply asserts that the claims have been limited to diseases characterized by an increased amount of organ specific free floating DNA; limiting individual to humans; limiting the methylation pattern to organ specific methylation; and adding an association step to compare results with normal individuals (p. 20 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The experimentation required by the skilled artisan is not merely routine experimentation but rather requires the skilled artisan to perform many experiments without a unknown expectation of success. Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a particular tissue, cell type, or organ without determining the differences in the methylation patterns between individuals. Such experimentation is not routine, but rather, requires the skilled artisan to perform many experiments on different samples with many intervening steps without a unknown of success. Therefore as discussed above, the experimentation required would be considered unpredictable based upon the lack of guidance in the specification and the unpredictable with such associations as exemplified by the cited art. As such the skilled artisan would have to perform undue extermination to determine if the methylation status of organ specific free floating DNA was correlative to disease or other physical

attributes of the sample.

Though at the time of filing the skill level was high the skilled artisan would have to perform more experimentation than simply determination of the methylation status of organ specific free floating DNA. Rather, the skilled artisan would have to further correlate the methylation status to a particular diseases state or to a disease state in general. As evidenced both by the specification teachings that particular disease must be confirmed by validation studies, and the unpredictability in the art to correlate methylation status and disease, the claimed method requires a high degree of unpredictable experimentation.

The claims are limited to diseases characterized by an increased amount of organ specific free floating DNA, however, this limitation is unpredictable. The specification teaches that particular disease must be confirmed by validation studies, and the unpredictability in the art to correlate methylation status and disease. The limitation of methylation pattern to organ specific methylation is unpredictable because Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a particular tissue, cell type, or organ without determining the differences in the methylation patterns between individuals. Though there is an association step to compare the results with normal individuals, the art teaches that physical attributes will affect methylation status of an individual and therefore it is unpredictable if the differences between the sample and the normal are due to disease or rather anther physical attribute (see the discussion of Raykan et al. and Liu et al.).

(I) The reply asserts that Claim 12 is not limited to a disease characterized by an increased amount of organ specific free floating DNA and should not be listed in the 35 USC 112/Enabmlematne rejection (p. 20 3rd paragraph).

These arguments have been fully reviewed and have been found persuasive and as such Claim 12 has been removed from the enablement rejection.

(J) The reply asserts that detection of disease with methylation patterns in free floating DNA is not unpredictable as the method has been used to confirm colon cancer marker Septin 9 (p. 21 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply does not specifically point to the argument presented for septin 9 in the previous amendments, however, the examiner is assuming that the reply is indication the arguments made in the reply filed 10/11/2007 on p. 13 and responded to in the Final rejection (1/03/2008). The reply points to evidence in the art of companies such as Abott and Epigenomics with circulating DNA such as Septin 9 as a diagnostic tool. This information is not in the cited reference and therefore the Attorney's arguments cannot take the place of evidence on the record. As stated in the MPEP, 2106 "Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that

factual affidavits could have provided important evidence on the issue of enablement."

In the instant case the reply points to diagnostic tools made by Abott and Epigenomics that have show diagnosis of patients. However, this does not support enablement of a predictive association of methylation patterns in circulating DNA to detection of any cellular proliferative disease or more broadly to any disease. Though some diagnostic methods do work, the correlation of methylation pattern to a disease is unpredictable and each individual association must be tested to determine predictability. As shown by Yang et al. and Raykan et al. methylation patterns are associated with age differences which would add unpredictability in the association of methylation status directly to disease. Further as shown in the reply the method is not towards merely a correlation of specific methylation marker to a specific disease, but a correlation of methylation pattern of organ to detect any organ based disease. Further the diagnostic tools made by Abott and Epigneomics are post-filing art and do not establish an enabling invention at the time the application was filed.

Claim Rejections - 35 USC § 112/Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6, 8-11, 13-14, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Claims are drawn to detecting the presence of a disease characterized by an increased amount of organ specific free floating DNA. Therefore the claims are drawn to detection of any disease characterized by an increased amount of organ specific free floating DNA.

The instant specification has not defined "a disease characterized by an increased amount of organ-specific free floating DNA". This term is an extremely large genus which would include any cancer disease, obesity, insulin-related disease, neurological disease, and ulceritis type disease, to describe a few. However, the specification has not provided guidance as to which of theses diseases are identifiably by the presence or increased amount of organ specific free floating DNA. Therefore the skilled artisan would not be able to determine which disease are encompassed by the phrase " a disease characterized by an increased amount of organ-specific free floating DNA" and functionally would be detectable by the presence or increased amount of organ specific free floating disease.

The specification provides examples wherein there is a detection of general inflammatory or cell proliferative diseases (Examples 1-4), however, the specification does not proved an example wherein a specific disease is detected only examples that indicate a disease might be present. Therefore these examples do not provide guidance to ascertain which disease is detectable by detecting the amount or presence of free floating DNA. Nor does the specification provide any guidance as to which

disease will be functionally detectable by detecting the amount or presence of free floating DNA.

Paredes-Zaglul et al. (Clinical Cancer Research Vol. 4 April 1998 p. 879) teaches that colon cancer spreads to the liver (p. 879 2nd column 1st paragraph). Therefore it would be unclear if an elevated free floating DNA amount in the liver would be indicative of a liver based disease or rather a colon based disease. Therefore the art teaches that not all disease characterized by increased organ specific free floating DNA can be detected by increased amount or presence of free floating DNA from a specific organ. In this example, the increased liver free floating DNA is not indicative of a liver disease, but rather a disease of the colon. Therefore it is unclear which disease in the genus of "diseases characterized by an increased amount of organ specific free floating DNA" would be detectable by the amount or presence of free floating DNA that originates from a particular organ.

Accordingly, the specification lacks written description of any species representative of the broadly claimed genus.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday

January 5, 2001.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of "diseases characterized by an increased amount of organ specific free floating DNA". As such, one of skill in the art would not recognize that applicant was in possession of the genus of "diseases characterized by an increased amount of organ specific free floating DNA" s encompassed by the broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. In order to have compact prosecution both a 35 USC 102 and a 35 USC 112/Enablement rejection has been made. The teachings in the specification appears to be commensurate with the teaching in Dennis et al, however the specification does not appear to add anything further to the teaching of the prior art. Therefore if the specification is found to be enabling the prior art is enabling and therefore the 35 USC 102 will be maintained. However if the specification is found not to be enabling the prior art provides no additional support for enablement.

8. Claims 1-4, 6, 8-11, 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Dennis et al. (US Patent Application Publication 2003/0044388 March 6, 2003 filed August 31, 2001).

With regard to Claim 1, Dennis et al. teaches obtaining a bodily fluid from a human sample (e.g. plasma or serum) (p. 2 paragraph 9). Dennis et al. teaches detecting the amount of DNA (e.g. in plasma and therefore free floating) that originates from a particular organ comprising analyzing a DNA methylation pattern p. 2 paragraph 9). Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the disease is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches that the determination in the differences between an organ donor and an organ recipient allows for the prediction of clinical progress of the transplantation recipient especially as regards to organ rejection (paragraph 9 p. 2). Therefore broadly interpreted the disease would encompass organ rejection. Dennis et al. teaches comparisons of the methylation status with control subjects (paragraph 43 p. 5).

With regard to Claim 2, the limitation difference between Claim 1 and Claim 2 is that there is a step of comparing the total amount of free floating DNA with the fraction of free floating DNA that originates from the organ. Dennis et al. teaches this limitation in such that the method teaches detection of the methylated gene (e.g. the fraction of the DNA that originates from the organ) and teaches that a further step of quantifying

the total concentration of DNA in the biological sample can be performed (p. 2 paragraph 9 and p. 5 paragraph 43).

With regard to Claim 2-4, Dennis et al. teaches a method wherein the sample is treated by heating and cooling and chemical treatment by the steps of harvesting and storing at -20C and using a chemical DNA extraction kit (paragraph 35-37 p. 4).

With regard to Claim 6, Dennis et al. teaches that the methylation patterns are characteristic for transplantation recipients and not control individuals (e.g. non-transplanted organs) (p. 5 paragraph 43).

With regard to Claim 8, Dennis et al. teaches a method using plasma or serum (p. 2 paragraph 9).

With regard to Claim 9, Dennis et al. teaches a method of methylation specific PCR wherein the DNA is subjected to chemical treatment to convert all unmethylated cytosines in the DNA into uracil but leaves positions of 5-methylatied cytosines unmodified (p. 3 paragraph 20).

With regard to Claim 10, the limitation difference between Claim 1 and Claim 10 is that there is a step comparing the presences of an increased level of free floating DNA with that of a normal control. Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the disease is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches comparisons of the methylation status with control subjects (paragraph 43 p. 5).

With regard to Claim 11, Dennis et al. teaches obtaining a bodily fluid from a human sample (e.g. plasma or serum) (p. 2 paragraph 9). Dennis et al. teaches step of quantifying the total concentration of DNA in the biological sample can be performed (p. 2 paragraph 9 and p. 5 paragraph 43). Dennis et al. teaches detecting the amount of DNA (e.g. in plasma and therefore free floating) that originates from a particular organ comprising analyzing a DNA methylation pattern p. 2 paragraph 9). Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the disease is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches comparisons of the methylation status with control subjects (paragraph 43 p. 5).

With regard to Claim 13, Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43).

With regard to Claim 14, Dennis et al. teaches using amplification procedures such as methylation specific PCR (p. 3 paragraph 20).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. It is noted that the 35 USC 103(a) rejection presented below is based upon the obviousness of performing methylation specific analysis on an array and therefore does not contradict the unpredictability discussed in the 35 USC 112/enablement rejection disclosed above.

11. Claims 12-14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dennis et al. (US Patent Application Publication 2003/0044388 March 6, 2003 filed August 31, 2001) in view of in view of Heiskanen et al. (Cancer Research 2000 Vol 60 p. 799).

With regard to Claim 12, Dennis et al. teaches obtaining a bodily fluid from a human sample (e.g. plasma or serum) (p. 2 paragraph 9). Dennis et al. teaches step of quantifying the total concentration of DNA in the biological sample can be performed (p. 2 paragraph 9 and p. 5 paragraph 43). Dennis et al. teaches detecting the amount of DNA (e.g. in plasma and therefore free floating) that originates from a particular organ comprising analyzing a DNA methylation pattern p. 2 paragraph 9). Dennis et al.

teaches a method of methylation specific PCR wherein the DNA is subjected to chemical treatment to convert all unmethylated cytosines in the DNA into uracil but leaves position 5-methylatied cytosines unmodified (p. 3 paragraph 20). Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the disease is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches that a further step of quantifying the total concentration of DNA in the biological sample (total free floating DNA) can be performed (p. 2 paragraph 9 and p. 5 paragraph 43).

With regard to Claim 13, Dennis et al. teaches determination of a disease characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43).

With regard to Claim 14, Dennis et al. teaches using amplification procedures such as methylation specific PCR (p. 3 paragraph 20).

However Dennis et al. does not teach performing the method steps with the total DNA bound to the surface.

Heiskanen et al. teaches a method of taking a target DNA and binding it to a surface (microarray) before using the target to detect expression levels (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Dennis et al. by binding the target DNA (free floating DNA) to a microarray as taught by Heiskanen et al. The ordinary artisan would be motivated to improve the method of Dennis et al. by binding

the target DNA (free floating DNA) to a microarray as taught by Heiskanen et al. because Heiskanen et al. teaches that by binding the DNA to a microarray parallel analysis of genomic DNA for expression analysis allows for a rapid approach to the identification of amplified genes in tumor cells. Therefore it would be obvious to rapidly identify any changes in the genes including methylation changes by using microarray parallel analysis because this method allows for the detection of many changes in the sample (e.g. methylation) to be detected simultaneously.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634

/Juliet C Switzer/

Primary Examiner, Art Unit 1634